THE RELATION OF THE DIET TO PELLAGRA.

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Pellagra has long been suspected of being caused by faulty diet, and the eating of maize, particularly moldy maize, has been considered by some students of the disease to be the specific cause. The studies of Dr. Goldberger of the Public Health Service have eliminated corn as a causative agent in the etiology of this disease. Funk in his enthusiasm over the "vitamine" hypothesis adopted the view that not only beri-beri but scurvy, rickets, and pellagra were each due to the lack of a specific "vitamine" in the diet. He further assumed, in order to explain the conflicting results in some of his experimental work, that other "vitamines" necessary for maintenance and for growth respectively are necessary in the food supply. We have attempted during the last two years to discover the exact nature of the deficiencies of such diets as are in common use among the people of the cotton mill villages in the South where pellagra is very common. We have employed what may properly be described as a biological method for the analysis of a food stuff or of mixtures of foods. This consists in feeding any foodstuff which is faulty in one or more respects to a group of animals, and in other experimental groups the same food supplemented with single or multiple food additions, such as pure protein, one or more pure mineral salts, one or more of the still unidentified dietary factors in the form of suitably prepared preparations. We have throughout these studies employed as a working hypothesis the assumption that the essential constituents of an adequate diet are protein of suitable quality and quantity, an adequate supply of the necessary inorganic elements in suitable combinations, an adequate energy supply in the form of protein, carbohydrate, and fat, and two as yet chemically unidentified dietary essentials which we have

designated "fat-soluble A" and "water-soluble B." The lack of the former leads to the development of a specific eye trouble which seems to be accurately described as a type of xerophthalmia. The factor water-soluble B is we believe identical wtih the substance which prevents or cures the disease beri-beri characterized by general paralysis which is common in the Orient.

Our experimental studies have now progressed so far as to enable us to assert with confidence that a satisfactory diet cannot be secured from mixtures containing any number of seeds or products derived from the milling of seeds together with tubers, edible roots, and meats. The vegetable foods which may be classed as seeds, tubers, and roots are all functionally storage organs, and their content of active protoplasm is relatively small in comparison with their bulk because of the large amount of reserve food material laid down in them. They may be sharply contrasted with the leaf of the plant, which except in special cases is not a repository for reserve proteins, carbohydrates, and fats, but represents, aside from its skeletal tissues, functionally active protoplasm. The leaf has very different dietary properties from those possessed by the tissues which are modified as storage organs, and in many instances at least represents complete foods for those types of animals whose digestive tracts are so capacious as to permit them to eat a sufficient amount of bulky material. We have been able to prepare fairly satisfactory diets for an omnivorous animal, the rat, from these two types of vegetable foods together, *i. e.,* leaves and seeds, but never from the group of vegetable foods which are functionally storage organs.

From this experience we have been led to differentiate sharply between two classes of foods which are usually collectively designated as vegetables. Leaves are constituted so as to correct the dietary deficiencies of the storage tissues, whereas the seeds, tubers, and roots fail to supplement mutually each other's deficiencies with respect to either the inorganic moiety or the fat-soluble A. They do in some degree mutually enhance the quality of each other's proteins, but to a lesser degree than we had supposed before the completion of a large amount of experimental work directed toward the

quantitative comparison of the protein mixtures derived from pairs of seeds in considerable number.

Mixtures of seeds, or of seeds, tubers, and roots, will in all cases require supplementing with respect to calcium, sodium, and chlorine among the inorganic elements, and fat-soluble A. In most such mixtures the quality of the proteins will likewise be sufficiently poor to require improvement before the optimum well-being can be secured.

We are now in possession of a considerable amount of knowledge concerning the distribution of the dietary factor, fat-soluble A, in animal tissues. The body fats of the ruminants will probably always be found to be richer in this substance than the body fats of the omnivora because of the greater intake of it in the food. Muscle tissue has been found to be very poor in fat-soluble A, but the fats from the glandular organs, *i. e.,* intracellular fats, are a good source of it. It follows, therefore, that muscle tissue such as round steak should not supplement mixtures of vegetable foods which belong to the storage organ group with respect to fat-soluble A, and in our experience this proves to be the case. The inorganic content of muscle tissue resembles in a general way that of the storage organs of plants except in its very low content of magnesium. It is too poor in calcium, and to a lesser degree in sodium and chlorine, to support the optimum well-being in an animal. Muscle tissue fails to supplement the seeds, tubers, and roots on the inorganic side. The protein content of muscle tissue is high and the proteins are probably of high biological value, and, except as respects palatability, it is only in improving the quality of the protein content of the ration that the addition of meats of this class enhances the value of a mixture of products derived from the storage organ group of plant products.

These considerations indicate the basis for our distinction between two groups of foodstuffs. One of these, which includes milk, eggs, and the leafy vegetables, we have designated as "protective foods," in order to call attention to their special importance in the diet. They are protective in that they are so constituted with respect to their inorganic content, content of fat-soluble A, and the quality of their proteins that they correct in great measure when

used in sufficient amounts the faults of the remainder of the food mixture irrespective of the extent to which it is derived from either seed, tuber, or root products. We have been able to plan satisfactory diets of naturally occurring foods only by the inclusion of one or more of these protective foods. The other group of natural foodstuffs includes all seeds and seed products, such as the cereal grains and their milling products (wheat flour, corn-meal, polished rice, etc.), the legume seeds, tubers, edible roots, nuts, fruits, and such cuts of meats as come from muscle tissue.

In all cases where we have attempted to correct the dietary deficiencies of a seed mixture by the addition of leaf only we have not secured results so good as with milk, especially with such amounts of leaf as would be acceptable in the human diet. The leafy foods are eaten by Europeans and Americans only in a very water rich condition, and it is difficult to secure the consumption of enough to correct the deficiencies in the remainder of the diet. With animals, when we have fed dry powdered mixtures containing as much as 25 to 40 per cent. of the diet derived from leaf and the remainder from plant products of the storage organ class, the nutrition has been very good in some instances, but not all combinations will be equally valuable. Eggs are decidedly poorer in calcium than are the leaves or milk, when only the part exclusive of the shell is considered. The shell serves as a source of lime to the developing chick. Eggs do not, therefore, supplement food mixtures derived from storage tissues with respect to calcium to the degree that milk and leafy vegetables do.

Even in such types of diet as contain one or more of the protective foods in fairly liberal amounts, it is certain that for such rapidly growing species of animals as the hog and rat the inorganic content is not entirely satisfactory, although it may be good enough to enable the animal to perform all the functions of growth and reproduction in a way which, in the absence of definite knowledge of what the species is capable of, we should regard as normal. We have been accustomed to regard as normal an achievement in vigor and well being both in man and animals which falls far short of that seen in exceptional cases. The most important inorganic deficiency in seed, tuber, and meat mixtures is calcium, and this is so pro-

nounced that we are of the opinion that even in those human dietaries in which such calcium-rich food as milk is used in fair liberality, the intake of calcium may be still below the optimum, and that a direct addition of this element in the form of the carbonate or lactate might be of distinct benefit in human nutrition except perhaps in those regions where the water is unusually rich in calcium salts. Since civilized man usually adds sodium chloride to his foods to suit the taste, the shortage of sodium and chlorine in the diet of man presents no problem. An addition of calcium could be most conveniently made to our foods through the use of a mixture of equal parts of common salt and of calcium carbonate in the kitchen and on the table.

A question which has never been answered to the satisfaction of physiologists is: How much protein should the diet contain in order to maintain physiological well being? At about the time when the question was being most discussed, the chemistry of the proteins was developed to a point which made it clear that there were great differences in the biological values of the proteins from different sources, depending on their yields of certain amino-acids. This makes futile any attempt to establish a particular intake of protein which may represent the minimum, optimum, or maximum amount consistent with maintenance of "normal" vitality and health. The quality of the proteins must be known before anything can be said about the amount of protein necessary. From biological tests we now know that the proteins of the pea or navy bean are worth only about half as much for growth in the rat as are equal amounts of proteins from one of the cereal grains, and that the latter have about half the value for the conversion into body proteins which can be shown for the proteins of milk. The relative values of the proteins from different sources, as well as the absolute values of certain of them, are just now becoming appreciated.

There are two opposing views regarding the amount of protein which will produce the best results. Those who advocate the low protein diet point to the "specific dynamic action" of protein, through which it stimulates metabolism. They believe that a high consumption of protein furnishes pabulum for the development of an excessive growth of putrefactive bacteria, with the result that

toxic or irritating products of the degradation of certain amino-acids are absorbed in amounts sufficient to cause damage to the tissues. It has been recommended that man should, in adult life, take only such an amount of protein as will cover the endogenous loss due to tissue metabolism, together with a not well-defined "margin of safety." The opponents of this view regard a liberal protein allowance as essential to vigor and aggressiveness, and point to the use of liberal amounts of meat by the peoples who have been characterized by greatest achievement. Among all the progressive peoples of the world the food supply is derived to a greater or less extent from daily products, and this portion rather than the meat eaten we have come to regard as of peculiar importance in improving the quality of the diet. In order to test this question we conducted a series of experiments, employing rats which were about nine months old, or about one fourth through the normal span of life for this species, and were in excellent nutritive condition. They were fed diets which were fairly satisfactory in all respects except that the protein content was not far from the actual amount required for the maintenance of body weight for a few weeks. We observed unmistakable signs that the vitality of the animals was rapidly lowered on such a dietary régime. This was shown especially by the rapid aging and short span of life. Even though the initial body weight was approximately maintained for a period of three months or more, distinct signs of aging were always apparent within five to ten months. Three months in the life of a rat correspond to about 8.4 per cent. of the average span of life. It can be readily appreciated that if harmful effects in corresponding degree follow the adherence by man to such low protein diets they would not become apparent within the time covered by any experiment yet conducted upon a diet squad, few of which have been restricted to any experimental diet beyond six months. A reputed satisfactory outcome of such experiments cannot be accepted as evidence that men on diets which furnish but a small margin of protein over the actual maintenance requirements are so nourished as best to promote health. Aging at two to four times the rate observed in the most satisfactorily nourished would escape observation in any experiment on man with which we are familiar.

The results of experiments with grown men restricted to experimental diets for a few weeks or months do not form a safe basis for drawing conclusions as to the quality of the foods employed. Certain conclusions may be warranted from general observations on children living on faulty diets, and important deductions may safely be drawn from the experiences of large groups of people living upon more or less restricted lists of foodstuffs. Beyond this we must be guided in human nutrition by the results of animal experimentation, in which the conditions can be made sufficiently rigid to bring into stronger contrast the faults of certain types of diets as contrasted with others. It is certain that the injurious effects of certain dietary practices are very real and yet not promptly apparent. The debilitating effects of faulty diets may vary in their severity from such as will produce polyneuritis or xerophthalmia or scurvy within a few weeks, at one extreme, to such as will cause nervousness and restlessness in varying degree, susceptibility to disease, and the acquisition of all those characters such as roughness of the skin, thinness and coarseness of hair, and attenuation of form which accompany the process of aging at a distinctly greater rate than would be the case were the diet of a highly satisfactory character.

We have much evidence that in case there is a close approximation of the actual physiological minimum for any factor during growth, such as one or more of the essential inorganic elements or one of the unidentified dietary essentials, lack of ability to meet the more strenuous demands of reproduction and the suckling of young will be observed, and the tendency will be great for the individual to be carried off suddenly either by disease, or, as frequently happens, by causes which are not readily determinable.

All our experience with diets of low protein content have indicated that animals do not remain in a state of optimum well-being even when the content of protein is sufficiently high to maintain in certain individuals the initial body weight over as much as 10 per cent. of the normal span of life. We believe that health and vigor are promoted by a liberal intake of protein of good quality better than by any diet in which there is a tendency towards parsimony with respect to this dietary factory. It should not be lost sight of, however, that there are other factors in nutrition which are of equal

importance with protein, and that if the optimum well-being is to be attained the diet must be rightly constituted with respect to all its parts. In addition to this the prompt elimination of the fecal residues is essential and is a great relief to the tissues of the entire body.

With an understanding such as we now have of the nature of the faults of diets of different types, and an appreciation of the fundamental importance of deriving the constituents of the diet from the right sources, this being of much greater importance than composition as revealed by chemical analysis, one is in a position to interpret the relation of pellagra to diet.

Goldberger has emphasized the fact that the diet of those living in districts in which pellagra is common is lacking in sufficient amounts of certain foodstuffs, especially milk, eggs, meats, and the legume seeds. In many instances bolted wheat flour, degerminated corn-meal, polished rice, sugar, syrups, or molasses, sweet potatoes, and meat, principally pork, form almost the entire list of foods eaten by families during the winter season, at the end of which new attacks of pellagra are regularly seen. From what has been said it will be evident that the diet of the pellagrous is deficient in four respects, and that the nature of these is well understood. They are the deficiencies of the plant products which belong to the storage organ group, but more pronounced because of the prominent place which milling products, which represent the endosperm of the seed, find in such diets. Products such as bolted flour, degerminated corn-meal, and polished rice are decidedly poorer in inorganic elements than are the seeds from which they are derived; their proteins appear to be of poorer quality than are those of the cell-rich structures near the periphery, or of the germ, and they are almost devoid of fat-soluble A and very poor in water-soluble B. Whereas diets derived from whole seeds, tubers, and edible roots contain sufficient phosphorus to meet the requirements of the most rapidly growing species of animal, such as the rat, and the limiting inorganic elements are calcium, sodium and chlorine, it may be that in diets in which the degerminated and decorticated cereal products are employed in liberal amounts, and where in addition starch, sugar and molasses are regularly used freely, phosphorus or iron or both may likewise become important deficiencies.

Goldberger attempted to solve the problem of whether pellagra is due to lack of something essential in the typical "pellagrous" diet by a direct experiment on man. He restricted men to a diet prepared from bolted wheat flour, degerminated corn-meal, polished rice, starch, sugar, syrup, pork fat, sweet potatoes, cabbage, collards, turnip greens and coffee, and at the end of five and a half months five of the eleven men who took this diet were diagnosed as exhibiting incipient signs of pellagra. That the disease was actually produced has been emphatically denied by McNeal.

In another experiment Goldberger and fifteen of his associates made heroic attempts to infect themselves with material from the lesions of pellagra, and with excreta from pellagrins, but without success. The experimenters were, however, taking a diet of good quality while these attempts were being made.

Still more convincing evidence that the diet is at least an important predisposing factor in the etiology of pellagra is furnished by the experience of Goldberger in improving the diets in institutions in which the disease was common. These diets were observed to consist largely of degerminated seed products, tubers or roots, and fat pork, together with minimal amounts of leafy vegetables, fruits, eggs, meats, and milk, and the legume seeds. On modifying the diets of orphanages and of an insane asylum by the addition of lean meat, milk, eggs, and peas or beans, the condition with respect to pellagra steadily improved, and the disease promptly disappeared. New cases were admitted from without and the sick were mingled with the well, but after the improvement of the diet no new cases developed.

Those who have had extensive experience with pellagra are in agreement in the matter of the fundamental importance of dietary treatment together with any other method of management of pellagrins, and the assertion has been made by Roussel that without dietary measures all remedies fail. The results obtained by Goldberger point clearly to the belief that the disease develops because of some one or more faults in the diet. They afford no basis, however, for judging as to the nature of these faults, whether they are in the nature of a lack of a sufficient amount of one or more chemically unidentified dietary essentials of a specific character, as is

known to be the case with beri-beri and the xerophthalmia of dietary origin, or whether pellagra may be the result of taking a diet faulty in respect to the quality or quantity of protein, relative shortage of one or more of the essential inorganic elements, or of the recognized unidentified dietary essentials as contributing factors.

In his earlier papers Goldberger expressed the view that: "On the whole, however, the trend of available evidence strongly suggests that pellagra will prove to be a 'deficiency' disease very closely related to beri-beri." Chittenden and Underhill reported the production in dogs of a condition suggestive of pellagra in man by restricting the animals for periods of from two to eight months to a diet of crackers, peas, and cottonseed oil. They formulated the conclusion that: "From the facts enumerated the conclusion seems tenable that the abnormal state may be referred to a deficiency of some essential dietary constituent or constituents, presumably belonging to the group of hitherto unrecognized but essential components of an adequate diet."

We have reported elsewhere the results of a study of the nature of the dietary faults of a mixture of bolted wheat flour, peas, and cottonseed oil, and found that it was an incomplete food, but that it was rendered complete for the support of normal growth in the young rat by the addition of purified protein, certain inorganic salts ($NaCl$ and $CaCO_3$) and fat-soluble A (in butter fat). It is of course not satisfactorily established that the condition produced in dogs by the diet of Chittenden and Underhill was actually the counterpart of pellagra in man, strikingly similar as the results appear. We hold the view that if the condition produced in the dogs of these investigators is actually to be regarded as experimental pellagra, it cannot be regarded as caused by the lack of an unidentified dietary essential, since the only one of these necessary for completing the diet (for the rat) is that contained in butter fat, and the latter substance is not curative for any condition resembling pellagra, but for a specific eye disease, xerophthalmia.

In his most recent studies Goldberger and his associates examined the diets of pellagrous and non-pellagrous families in villages in South Carolina, and found that the diet of the non-pellagrous contained more milk, fresh meats, eggs, butter, and cheese than did

the diets of pellagrous families, and that calorific value of the diets of the former households was somewhat higher than of the latter. Animal proteins were eaten more liberally and cereal proteins were eaten less abundantly by the non-pellagrous than by the pellagrous households. The pellagrous households had a distinctly smaller supply of fat-soluble A, and a somewhat smaller supply of water-soluble B than did the non-pellagrous, and the inorganic content of the diets of the latter were of less satisfactory character than those of the former households. We do not regard a moderate shortage of one or another of the chemically unidentified dietary factors as of greater gravity than faulty character in any other dietary factor. Our studies of the several foodstuffs lead us to agree with Goldberger's interpretation of the quality of the diets of pellagrous and non-pellagrous households in all respects.

From the observations which we have made concerning the chemical factors which the diet must contain in order to be adequate for the support of growth in the young, or the maintenance of physiological well-being in the adult, together with the results of our studies of the qualities of each of the more important kinds of natural foodstuffs, we are not able to account for the etiology of pellegra on the assumption that it is a disease which is due to the lack of a specific substance or substances of unknown chemical nature, as are without question beri-beri and xerophthalmia. This follows from the fact that, with the exceptions of certain manufactured food products which are derived from the endosperm of the decorticated grains, any natural foodstuffs of the class of seeds, tubers, edible roots, or leafy parts of the plant, are so constituted that they can be supplemented by means of three kinds of purified food additions of known nature: viz., protein, certain salts, and fat-soluble A, so as to be complete for the nutrition of the young rat throughout the growing period. This has been demonstrated to be true not only for each of the ordinary human foods but likewise for such mixtures as form the monotonous diets of the pellagrous.

It is necessary, therefore, that we choose between two alternatives in arriving at an opinion concerning the etiology of pellagra. We have the assurances of Goldberger and his associates that a diet such as that described on page 49, and having the qualities described

in the preceding paragraph, has produced incipient pellagra experimentally in man, but this claim has been disputed by other competent observers. In our experimental work with the diet of peas, crackers (wheat flour and fat), and cottonseed oil, which in the experience of Chittenden and Underhill produced in dogs a condition resembling pellagra in man, produced in rats only general malnutrition, without the skin changes, diarrhea, or pathological changes in the mucosa of the alimentary tract. Are we to accept the view that pellagra is actually produced by a deficiency of something necessary to the normal nutrition of man but not necessary for the rat? The possibility that the dogs of Chittenden and Underhill were infected is not excluded, and an infectious agent may well have established itself in animals restricted to a diet so faulty as one derived from crackers (wheat flour and fat), peas, and cottonseed oil. Goldberger seems to have safeguarded his experimental men against infection, and it is unfortunate that a sufficient number of undisputed authorities were not called into consultation to forestall the possibility of a question arising concerning the accuracy of the diagnosis of pellagra, such as McNeal has raised.

We are left in the situation which has arisen in the discussion of the etiology of scurvy. It has been clearly shown that there is no difficulty in repeating the experimental work which demonstrated that a guinea pig will develop severe scurvy (or some syndrome resembling it) on a number of diets on which the rat will thrive during the growing period. Does this mean that the guinea pig requires one or more chemical complexes for its nutrition that are dispensable to the rat? There is no doubt that the guinea pig normally takes a diet rich in succulent vegetables, and which produces bulky, easily eliminable feces. The rat and swine, as well as man, thrive on certain diets which leave little indigestible residue. Such special requirements in the guinea pig make it next to impossible to compare this species with man or the rat in similar dietary studies. The experimental data obtained with the guinea pig must be used with caution in reasoning concerning the etiology of human scurvy.

In our attempts to produce in animals a condition analogous to pellagra in man we have not been successful, but have observed only a generalized poor condition instead. The evidence is practically

nil that Chittenden and Underhill's dogs suffered all the pathological changes which they record solely as the result of chemical faults in the diet. Our experiments with their diet show it to be incapable of maintaining satisfactory nutrition because of faults in the dietary factors. The possibility of an infection in their animals is not excluded, and is indeed rendered probable if we grant that lowered vitality predisposes to infection. These reasons together with the lack of positive proof that the men restricted in Goldberger's experiments to a diet similar to that described were actually developing pellagra, warrant, we believe, our accepting as probably correct the conclusions of the Thompson-McFadden Commission and of Jobling and Peterson that pellagra is caused by an infectious agent, and that unless it has been introduced into a district there may develop such a condition of lowered vitality from faulty diet or other debilitating influence as would predispose one to an attack, without the appearance of the disease. The debilitating effects on animals of diets derived from cereals, tubers, roots, and any food products formed from the milling of grains together with legume seeds and meats, are so striking that we believe similar diets would produce in man a susceptibility to infectious diseases such as tuberculosis or pellagra. We have come to hold the view, as the result of our studies of diets of the type common in pellagrous households, that the predisposing influence for both is in general the same, and the character of the unsanitary conditions surrounding the individual may determine which of these two diseases he will develop.

From the studies which we have described elsewhere we are enabled to point out definitely the relative values of several foods as correctives in the diet of the pellagrous. Hitherto the legume seeds and lean meat were classed with milk and eggs in this respect, and nothing was said about the unique qualities of the leafy vegetables as supplements for food mixtures derived from plant products of the storage organ group. It is clear that the most important food to be recommended for consumption in pellagrous districts is milk, because of its cheapness as compared with the same protective value in foods from other sources and its threefold corrective character as contrasted with meat which enhances the type of diet found in the pellagrous household only with respect to the protein factor, and

eggs which are not so good as milk because of their lower calcium content. The legume seeds, notwithstanding their high content of protein, are without any appreciable value for improving the diets which predispose to pellagra, because of the poor quality of their protein and their failure to supplement a diet derived from vegetable foods of the storage tissue class in other respects.

Both meats and eggs are more expensive sources of protection against faulty diet than milk. An effective campaign of education should be conducted in all districts where diets of a character likely to predispose to pellagra are common, informing the people about the great benefits to health from regular and very liberal use of leafy vegetables. This would be a movement toward the establishment of dietary practices resembling those of the more nearly vegetarian groups of Chinese and Japanese, and if in addition the inclusion of a suitable amount of milk in the diet can be secured, not only would pellagra disappear, but the general health of the people would be promoted.

The prevalence of pellagra in certain parts of the South rather than in other sections of the country is probably closely connected with the development of the modern milling industry. This places in the grocery store the degerminated and decorticated part of the grain. The rise of the sugar industry offers for human consumption both sugar and molasses in quantities unheard of until recent years.

The widespread practice of growing a cash crop (cotton), and of depending on the retail store for the greater part of the food supply rather than of engaging in diversified farming appears to be in great measure responsible for the existence of pellagra. The food products which can be handled commercially without hazard are not in general satisfactory foodstuffs unless properly supplemented with certain others which correct their deficiencies.

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